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(54) **Title:** COMPOUND

(57) **Abstract:** The invention provides a pharmaceutical product, kit or composition comprising a first active ingredient which is 3-(2-Chloro-3-((4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)-N-cyclopentyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl(ethylamino)ethyl)propanamide or a salt thereof, and a second active ingredient selected from: a non-steroidal Glucocorticoid Receptor (GR Receptor) Agonist; an antioxidant; a CCR1 antagonist; a chemokine antagonist (not CCR1); a corticosteroid; a CRTh2 antagonist; a DP1 antagonist; an Histone Deacetylase activator; an IKK2 kinase inhibitor; a COX inhibitor; a lipoxygenase inhibitor; a leukotriene receptor antagonist; an MPO inhibitor; a PDE4 inhibitor; a PPAR γ agonist; a protease inhibitor; a p38 inhibitor, a selective glucocorticoid receptor agonist (SEGRA), a Statin; a thromboxane antagonist; a vasodilator; or, an ENAC blocker (Epithelial Sodium-channel blocker); and its use in the treatment of respiratory disease.



COMPOUND

The present invention relates to a combination of two or more pharmaceutically active substances for use in the treatment of respiratory diseases (for example chronic obstructive pulmonary disease (COPD) or asthma).

The essential function of the lungs requires a fragile structure with enormous exposure to the environment, including pollutants, microbes, allergens, and carcinogens. Host factors, resulting from interactions of lifestyle choices and genetic composition, influence the response to this exposure. Damage or infection to the lungs can give rise to a wide range of diseases of the respiratory system (or respiratory diseases). A number of these diseases are of great public health importance. Respiratory diseases include Acute Lung Injury, Acute Respiratory Distress Syndrome (ARDS), occupational lung disease, lung cancer, tuberculosis, fibrosis, pneumoconiosis, pneumonia, emphysema, Chronic Obstructive Pulmonary Disease (COPD) and asthma.

Among the most common of the respiratory diseases is asthma. Asthma is generally defined as an inflammatory disorder of the airways with clinical symptoms arising from intermittent airflow obstruction. It is characterised clinically by paroxysms of wheezing, dyspnea and cough. It is a chronic disabling disorder that appears to be increasing in prevalence and severity. It is estimated that 15% of children and 5% of adults in the population of developed countries suffer from asthma. Therapy should therefore be aimed at controlling symptoms so that normal life is possible and at the same time provide basis for treating the underlying inflammation.

COPD is a term which refers to a large group of lung diseases which can interfere with normal breathing. Current clinical guidelines define COPD as a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases. The most important contributory source of such particles and gases, at least in the western world, is tobacco smoke. COPD patients have a variety of symptoms, including cough, shortness of breath, and excessive production of sputum; such symptoms arise from dysfunction of a number of cellular compartments, including neutrophils, macrophages, and epithelial cells. The two most important conditions covered by COPD are chronic bronchitis and emphysema.

Chronic bronchitis is a long-standing inflammation of the bronchi which causes increased production of mucous and other changes. The patients' symptoms are cough and expectoration of sputum. Chronic bronchitis can lead to more frequent and severe respiratory infections, narrowing and plugging of the bronchi, difficult breathing and disability.

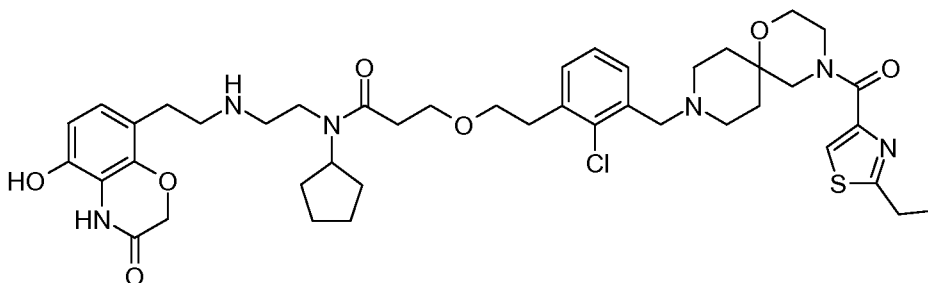
Emphysema is a chronic lung disease which affects the alveoli and/or the ends of the smallest bronchi. The lung loses its elasticity and therefore these areas of the lungs become enlarged. These enlarged areas trap stale air and do not effectively exchange it with fresh air. This results in difficult breathing and may result in insufficient oxygen being delivered to the blood. The predominant symptom in patients with emphysema is shortness of breath.

Therapeutic agents used in the treatment of respiratory diseases include corticosteroids. Corticosteroids (also known as glucocorticosteroids or glucocorticoids) are potent anti-inflammatory agents. Whilst their exact mechanism of action is not clear, the end result of corticosteroid treatment is a decrease in the number, activity and movement of inflammatory cells into the bronchial submucosa, leading to decreased airway responsiveness. Corticosteroids may also cause reduced shedding of bronchial epithelial lining, vascular permeability, and mucus secretion. Whilst corticosteroid treatment can yield important benefits, the efficacy of these agents is often far from satisfactory, particularly in COPD. Moreover, whilst the use of steroids may lead to therapeutic effects, it is desirable to be able to use steroids in low doses to minimise the occurrence and severity of undesirable side effects that may be associated with regular administration. Recent studies have also highlighted the problem of the acquisition of steroid resistance amongst patients suffering from respiratory diseases. For example, cigarette smokers with asthma have been found to be insensitive to short term inhaled corticosteroid therapy, but the disparity of the response between smokers and non-smokers appears to be reduced with high dose inhaled corticosteroid (Tomlinson *et al.*, Thorax 2005; 60:282-287).

A further class of therapeutic agent used in the treatment of respiratory diseases are bronchodilators. Bronchodilators may be used to alleviate symptoms of respiratory diseases by relaxing the bronchial smooth muscles, reducing airway obstruction, reducing lung hyperinflation and decreasing shortness of breath. Types of bronchodilators in clinical use include β_2 adrenoceptor agonists, muscarinic receptor antagonists and

methylxanthines. Bronchodilators are prescribed mainly for symptomatic relief and they are not considered to alter the natural history of respiratory diseases.

3-(2-Chloro-3-((4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)-N-cyclopentyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo [b][1,4] oxazin-8-yl)ethylamino)ethyl)propanamide



is a dual β_2 adrenoceptor agonist/ M_3 receptor antagonist (MABA) compound and is comprised in PCT patent application no. PCT/GB2010/051242 as Example 33.

Combination products comprising a β_2 adrenoceptor agonist and a corticosteroid are available. One such product is a combination of budesonide and formoterol fumarate (marketed by AstraZeneca under the tradename Symbicort®), which has proven to be effective in controlling asthma and COPD, and improving quality of life in many patients.

In view of the complexity of respiratory diseases such as asthma and COPD, it is unlikely that any one mediator can satisfactorily treat a respiratory disease alone.

Moreover, whilst combination treatments using a β_2 adrenoceptor agonist and a corticosteroid deliver significant patient benefits, there remains a medical need for new therapies against respiratory diseases such as asthma and COPD, in particular for therapies with disease modifying potential.

Accordingly, the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient which is 3-(2-Chloro-3-((4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)-N-cyclopentyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo [b][1,4] oxazin-8-yl)ethylamino)ethyl)propanamide or a salt thereof, and a second active ingredient selected from:

an Adenosine A2A receptor antagonist;

an anti-infective;

a non-steroidal Glucocorticoid Receptor (GR Receptor) Agonist;

- an antioxidant;
- a CCR1 antagonist;
- a chemokine antagonist (not CCR1);
- a corticosteroid;
- 5 a CRTh2 antagonist;
- a DP1 antagonist;
- a formyl peptide receptor antagonist;
- a Histone Deacetylase activator;
- a chloride channel hCLCA1 blocker
- 10 an Epithelial sodium channel blocker (ENAC blocker)).
- an Inter-cellular adhesion molecule 1 blocker (ICAM blocker);
- an IKK2 kinase inhibitor;
- a JNK kinase inhibitor;
- a cyclooxygenase inhibitor (COX inhibitor);
- 15 a lipoxygenase inhibitor;
- a leukotriene receptor antagonist;
- a MEK-1 kinase inhibitor;
- a myeloperoxidase inhibitor (MPO inhibitor);
- a phosphodiesterase PDE4 inhibitor;
- 20 a phosphatidylinositol 3 (PI3)-kinase γ inhibitor (PI 3 kinase γ inhibitor)
- a peroxisome proliferator activated receptor agonist (PPAR γ agonist);
- a protease inhibitor;
- a p38 inhibitor
- a retinoic acid receptor modulator (RAR γ modulator)
- 25 a selective glucocorticoid receptor agonist (SEGRA),
- a Statin;
- a thromboxane antagonist; or
- a vasodilator.

The first active ingredient, which is 3-(2-Chloro-3-((4-(2-ethylthiazole-4-carbonyl)-
 30 1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)-N-cyclopentyl-N-(2-(2-(5-
 hydroxy-3-oxo-3,4-dihydro-2H-benzo [b][1,4] oxazin-8-yl)ethylamino)ethyl)propanamide
 or a salt thereof, may be in the form of a solvate (such as a hydrate).

A suitable salt of 3-(2-Chloro-3-((4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)-N-cyclopentyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo [b][1,4] oxazin-8-yl)ethylamino)ethyl)propanamide is, for example, a sulphate or a hydrochloride, hydrobromide, trifluoroacetate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulphonate, *p*-toluenesulphonate, bisulphate, benzenesulphonate, ethanesulphonate, malonate, xinafoate, ascorbate, oleate, nicotinate, saccharinate, adipate, formate, glycolate, L-lactate, D-lactate, aspartate, malate, L-tartrate, D-tartrate, stearate, 2-furoate, 3-furoate, napadisylate (naphthalene-1,5-disulfonate or naphthalene-1-(sulfonic acid)-5-sulfonate), edisylate (ethane-1,2-disulfonate or ethane-1-(sulfonic acid)-2-sulfonate), isethionate (2-hydroxyethylsulfonate), 2-mesitylenesulphonate, 2-naphthalenesulphonate, 2,5-dichlorobenzenesulphonate, D-mandelate, L-mandelate, cinnamate, benzoate, adipate, esylate, malonate, mesitylate (2-mesitylenesulphonate), napsylate (2-naphthalenesulfonate), camsylate (camphor-10-sulphonate, for example (1S)-(+)-10-Camphorsulfonic acid salt), formate, glutamate, glutarate, glycolate, hippurate (2-(benzoylamino)acetate), orotate, xylate (*p*-xylene-2-sulphonate), pamoic (2,2'-dihydroxy-1,1'-dinaphthylmethane-3,3'-dicarboxylate), palmitate or furoate. It is to be understood for the avoidance of confusion that salts may exist in varying stoichiometries, for example, but not limited to, hemi-, mono-, and di-, and that the invention encompasses all such forms.

In one aspect the present invention provides a pharmaceutical product wherein the first active ingredient is 3-(2-Chloro-3-((4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)-N-cyclopentyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo [b][1,4] oxazin-8-yl)ethylamino)ethyl)propanamide or a salt thereof.

The first and second active ingredients can be administered simultaneously (either in a single pharmaceutical preparation {that is, the active ingredients are in admixture} or via separate preparations), or sequentially or separately via separate pharmaceutical preparations.

An Adenosine A2A receptor antagonist is, for example, a compound such as UK-432097.

An antiinfective is, for example, an antibiotic such as Amoxicillin, Doxycycline, Trimethoprim sulpha, or a Cephalosporin.

A non-steroidal glucocorticoid receptor (GR) agonist is, for example, a compound disclosed in WO2008/076040, for example 2,2,2-trifluoro-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]acetamide; N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(4-methylsulfonylphenyl)propan-2-yl]-2-hydroxy-acetamide; N-[(1R*,2S*)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(6-methoxypyridin-3-yl)propan-2-yl]cyclopropanecarboxamide; (2S)-N-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-phenyl-propan-2-yl]-2-hydroxy-propanamide; 2,2,2-trifluoro-N-[(2S*,3S*)-3-[1-(4-fluorophenyl)indazol-5-yl]oxy-4-phenoxy-butan-2-yl]acetamide; N'-[(1R,2S)-1-[1-(4-fluorophenyl)indazol-5-yl]oxy-1-(3-methoxyphenyl)propan-2-yl]-N-propan-2-yl-oxamide, or a pharmaceutically acceptable salt thereof.

An antioxidant is, for example, Allopurinol, Erdosteine, Mannitol, N-acetyl cysteine choline ester, N-acetyl cysteine ethyl ester, N-Acetylcysteine, N-Acetylcysteine amide or Niacin.

A CCR1 antagonist is, for example, a compound disclosed in WO2001/062728 or WO2001/098273, or a pharmaceutically acceptable salt thereof (such as a hydrochloride, trifluoroacetate, sulphate, (hemi)fumarate, benzoate, furoate or succinate salt).

Also, a CCR1 antagonist is, for example, N-{2-[(2S)-3-{[1-(4-chlorobenzyl)piperidin-4-yl]amino}-2-hydroxy-2-methylpropyl]oxy]-4-hydroxyphenyl}acetamide, also named as 4-({(2S)-3-[2-(acetylamino)-5-hydroxyphenoxy]-2-hydroxy-2-methylpropyl}ammonio)-1-(4-chlorobenzyl)piperidine (see WO 2003/051839), or, 2-{2-Chloro-5-[(2S)-3-(5-chloro-1'H,3H-spiro[1-benzofuran-2,4'-piperidin]-1'-yl)-2-hydroxypropyl]oxy}-4-[(methylamino)carbonyl]phenoxy}-2-methylpropanoic acid (see PCT publication no. WO 2008/010765), or a pharmaceutically acceptable salt thereof (for example a hydrochloride, sulphate, (hemi)fumarate, benzoate, furoate or succinate salt).

A chemokine antagonist (other than a CCR1 antagonist), for example, 656933 (N-(2-bromophenyl)-N'-(4-cyano-1H-1,2,3-benzotriazol-7-yl)urea), 766994 (4-({[[(2R)-4-(3,4-dichlorobenzyl)morpholin-2-yl]methyl]amino}carbonyl)-amino}methyl)benzamide), CCX-282, CCX-915, Cyanovirin N, E-921, INCB-003284, INCB-9471, Maraviroc, MLN-3701, MLN-3897, T-487 (N-{1-[3-(4-ethoxyphenyl)-4-oxo-3,4-dihydropyrido[2,3-d]pyrimidin-2-yl]ethyl}-N-(pyridin-3-ylmethyl)-2-[4-(trifluoromethoxy)phenyl]acetamide) or Vicriviroc.

A chloride channel hCLCA1 blocker is, for example, as disclosed in WO2006/091112, WO2004/113286 and WO2001/038530.

A corticosteroid is, for example, Alclometasone dipropionate, Amelometasone, Beclomethasone dipropionate, Budesonide, Butixocort propionate, Ciclesonide, Clobetasol propionate, Desisobutyrylciclesonide, Etiprednol dicloacetate, Fluocinolone acetonide, 5 Fluticasone Furoate, Fluticasone propionate, Loteprednol etabonate (topical) or Mometasone furoate.

A glucocorticosteroid compound is (1R,3aS,3bS,10aR,10bS,11S,12aS)1-
{[(cyanomethyl)sulfanyl]carbonyl}-7-(4-fluorophenyl)-11-hydroxy-10a,12a-dimethyl-
10 1,2,3,3a,3b,4,5,7,10,10a,10b,11,12,12a-tetradecahydrocyclopenta[5,6]naphtho[1,2-
f]indazol-1-yl furan-2-carboxylate. The compound is disclosed in WO-2009/044200.

A CRTh2 antagonist is, for example, a compound from WO 2004/106302, WO2004/089885, WO2005/018529 or WO2007/039741.

A DP1 antagonist is, for example, L888839 or MK0525.

15 An ENAC (Epithelial Sodium-channel blocker) is, for example, Amiloride, Benzamil, Triamterene, 552-02, PSA14984, PSA25569, PSA23682, AER002, Parion P-522 or a compound from WO2008031048.

A formyl peptide receptor antagonist is, for example, a compound from WO2007/144198.

20 A histone deacetylase activator is, for example, ADC4022, Aminophylline, a Methylxanthine or Theophylline.

An ICAM blocker is, for example, an anti-ICAM-1 monoclonal antibody (MAb) 1A6 from Antimicrobial Agents and Chemotherapy 2003, 47, 1503-1508.

An IKK2 inhibitor is, for example, 2-{[2-(2-Methylamino-pyrimidin-4-yl)-1H-indole-5-carbonyl]-amino}-3-(phenyl-pyridin-2-yl-amino)-propionic acid or a compound
25 as disclosed in WO 01/58890, WO 03/010158, WO 03/010163, WO 04/063185, WO 04/063186.

A JNK inhibitor is, for example, a compound from WO2005/003123 or WO2003/051277.

30 A COX inhibitor is, for example, Celecoxib, Diclofenac sodium, Etodolac, Ibuprofen, Indomethacin, Meloxicam, Nimesulide, OC1768, OC2125, OC2184, OC499, OCD9101, Parecoxib sodium, Piceatannol, Piroxicam, Rofecoxib or Valdecoxib.

A lipoxygenase inhibitor is, for example, Ajulemic acid, Darbufelone, Darbufelone mesilate, Dexibuprofen lysine (monohydrate), Etalocib sodium, Licofelone, Linazolast, Lonapalene, Masoprocol, MN-001, Tepoxalin, UCB-35440, Veliflapon, ZD-2138, ZD-4007 or Zileuton ((±)-1-(1-Benzo[b]thien-2-ylethyl)-1-hydroxyurea)

5 A leukotriene receptor antagonist is, for example, Ablukast, Iralukast (CGP 45715A), Montelukast, Montelukast sodium, Ontazolast, Pranlukast, Pranlukast hydrate (mono Na salt), Verlukast (MK-679) or Zafirlukast.

A MEK-1 inhibitor is, for example, a compound disclosed in WO2007123939, WO2007025090 or WO2005051906.

10 An MPO Inhibitor is, for example, a Hydroxamic acid derivative (N-(4-chloro-2-methyl-phenyl)-4-phenyl-4-[[4-propan-2-ylphenyl)sulfonylamino]methyl]piperidine-1-carboxamide), Piceatannol or Resveratrol, or a compound disclosed within US7425560, WO2003/089430, WO2006/062465 and WO2007/120098.

p38 inhibitors are, for example, a compound from WO 2005/042502, 681323, 15 856553, AMG548 (2-[[[(2S)-2-amino-3-phenylpropyl]amino]-3-methyl-5-(2-naphthalenyl)-6-(4-pyridinyl)-4(3H)-pyrimidinone), Array-797, AZD6703, Doramapimod, KC-706, PH 797804, R1503, SC-80036, SCIO469, 6-chloro-5-[[[(2S,5R)-4-[(4-fluorophenyl)methyl]-2,5-dimethyl-1-piperazinyl]carbonyl]-N,N,1-trimethyl- α -oxo-1*H*-indole-3-acetamide, VX702 or VX745 (5-(2,6-dichlorophenyl)-2-(phenylthio)-6H-pyrimido[1,6-b]pyridazin-6-
20 one). *N*-cyclopropyl-3-fluoro-4-methyl-5-[3-[[1-[2-[2-(methylamino)ethoxy]phenyl]cyclopropyl]amino]-2-oxo-1(2*H*)-pyrazinyl]-benzamide is exemplified in WO2009/001132.

A PI 3 kinase γ inhibitor is, for example, a compound from WO2005/105801, WO2003/072557, and WO2007/082956.

25 A PPAR γ agonist is, for example, Pioglitazone, Pioglitazone hydrochloride, Rosiglitazone Maleate, Rosiglitazone Maleate ((-)-enantiomer, free base), Rosiglitazone maleate/Metformin hydrochloride or Tesaglitazar.

A Protease Inhibitor is, for example, Alpha1-antitrypsin proteinase Inhibitor, EPI-HNE4, UT-77, ZD-0892 or a compound from WO 2006/004532, WO 2005/026123, WO 30 2002/0744767 or WO 22002/074751; or a TACE Inhibitor (for example DPC-333, Sch-709156 or Doxycycline);. inhibitors of cathepsins for example inhibitors of cathepsin S (for example as disclosed in WO2002/14314), cathepsin L (for example as described

within Bioorg. Med. Chem. 2004,12, 4081), cathepsin K (for example WO 2001/47886), cathepsin B (for example tokaramide A and leupetin) and cathepsin C (dipeptidyl peptidase 1) (for example a compound from WO 2005/000800); inhibitors of neutrophil elastase, for example as disclosed in WO2005/026123 and WO2007/129963 (for example 6-[1-(4-cyanophenyl)-1H-pyrazol-5-yl]-N,5-dimethyl-3-oxo-4-[3-(trifluoromethyl)phenyl]-3,4-dihydropyrazine-2-carboxamide) and inhibitors of matrix metallo proteinases (for example ABT-518 or Ro-32-7315).

A RAR γ modulator (Retinoic acid gamma receptor modulator) is, for example, palovarotene (R667), a compound disclosed in WO2008064136 (agonists) or WO2006066978 (antagonists).

A selective glucocorticoid receptor agonist (SEGRA) is, for example, selected from the compounds exemplified in WO2008/076048 or WO 2009/142571.

A Statin is, for example, Atorvastatin, Lovastatin, Pravastatin, Rosuvastatin or Simvastatin.

A Thromboxane Antagonist is, for example, Ramatroban or Seratrodast.

A Vasodilator is, for example, A-306552, Ambrisentan, Avosentan, BMS-248360, BMS-346567, BMS-465149, BMS-509701, Bosentan, BSF-302146 (Ambrisentan), Calcitonin Gene-related Peptide, Daglutril, Darusentan, Fandosentan potassium, Fasudil, Iloprost, KC-12615 (Daglutril), KC-12792 2AB (Daglutril), Liposomal treprostinil, PS-433540, Sitaxsentan sodium, Sodium Ferulate, TBC-11241 (Sitaxsentan), TBC-3214 (N-(2-acetyl-4,6-dimethylphenyl)-3-[[4-chloro-3-methyl-5-isoxazolyl]amino]sulfonyl]-2-thiophenecarboxamide), TBC-3711, Trepidil, Treprostinil diethanolamine or Treprostinil sodium.

A PDE4 inhibitor is, for example, 6-fluoro-N-((1s,4s)-4-(6-fluoro-2,4-dioxo-1-(4'-(piperazin-1-ylmethyl)-biphenyl-3-yl)-1,2-dihydropyrido[2,3-d]pyrimidin-3(4H)-yl)cyclohexyl)imidazo[1,2-a]pyridine-2-carboxamide (as disclosed in WO2008084223), or a salt thereof (for example a (1S)-(+)-10-Camphorsulfonic acid or trihydrochloride salt).

All the above second *et seq* active ingredients may be in the form of solvates, for example hydrates.

In one particular aspect the present invention provides a pharmaceutical product comprising the first and second active ingredients in admixture. Alternatively, the pharmaceutical product may, for example, be a kit comprising a preparation of the first

active ingredient and a preparation of the second active ingredient and, optionally, instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

The first active ingredient and the second active ingredient of the pharmaceutical product of the present invention may be administered simultaneously, sequentially or separately to treat respiratory diseases. By simultaneously is meant that the active ingredients are in admixture, or they could be in separate chambers of the same inhaler. By sequential it is meant that the active ingredients are administered, in any order, one immediately after the other. They still have the desired effect if they are administered separately, but when administered in this manner they are generally administered less than 4 hours apart, conveniently less than two hours apart, more conveniently less than 30 minutes apart and most conveniently less than 10 minutes apart, for example less than 10 minutes but not one immediately after the other.

The active ingredients may be delivered to the lung and/or airways via oral administration in the form of a solution, suspension, aerosol or dry powder formulation. These dosage forms will usually include one or more pharmaceutically acceptable ingredients which may be selected, for example, from an adjuvant, carrier, binder, lubricant, diluent, stabilising agent, buffering agent, emulsifying agent, viscosity-regulating agent, surfactant, preservative, flavouring or colorant. The active ingredients of the present invention may also be administered by oral or parenteral (e.g. intravenous, subcutaneous, intramuscular or intraarticular) administration using conventional systemic dosage forms, such as tablets, capsules, pills, powders, aqueous or oily solutions or suspensions, emulsions and sterile injectable aqueous or oily solutions or suspensions. As will be understood by those skilled in the art, the most appropriate method of administering the active ingredients is dependent on a number of factors.

In another embodiment the first and second active ingredients are administered via a single pharmaceutical composition (that is, the first and second active ingredients are in admixture). Therefore, the present invention further provides a pharmaceutical composition comprising, in admixture, a first active ingredient which is 3-(2-Chloro-3-((4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)-N-cyclopentyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo [b][1,4] oxazin-8-yl)ethylamino)ethyl)propanamide or a salt thereof (such as the hydrochloride or L-tartaric

acid salt), and a second active ingredient as defined above. The pharmaceutical composition optionally further comprises a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions of the present invention can be prepared by mixing the first active ingredient with the second active ingredient and a pharmaceutically acceptable adjuvant, diluent or carrier. Therefore, in a further aspect of the present invention there is provided a process for the preparation of a pharmaceutical composition, which comprises mixing the first and second active ingredients and a pharmaceutically acceptable adjuvant, diluent or carrier.

It will be understood that the therapeutic dose of each active ingredient administered in accordance with the present invention will vary depending upon the particular active ingredient employed, the mode by which the active ingredient is to be administered, and the condition or disorder to be treated.

In one embodiment of the present invention, the first active ingredient is administered via inhalation. When administered via inhalation the dose of the first active ingredient (that is 3-(2-Chloro-3-((4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)-N-cyclopentyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo [b][1,4] oxazin-8-yl)ethylamino)ethyl)propanamide in: salt form, solvate form, or, solvate of salt form) will generally be in the range of from 0.1 microgram (μg) to 5000 μg , 0.1 to 1000 μg , 0.1 to 500 μg , 0.1 to 100 μg , 0.1 to 50 μg , 0.1 to 5 μg , 5 to 5000 μg , 5 to 1000 μg , 5 to 500 μg , 5 to 100 μg , 5 to 50 μg , 5 to 10 μg , 10 to 5000 μg , 10 to 1000 μg , 10 to 500 μg , 10 to 100 μg , 10 to 50 μg , 20 to 5000 μg , 20 to 1000 μg , 20 to 500 μg , 20 to 100 μg , 20 to 50 μg , 50 to 5000 μg , 50 to 1000 μg , 50 to 500 μg , 50 to 100 μg , 100 to 5000 μg , 100 to 1000 μg or 100 to 500 μg . The dose will generally be administered from 1 to 4 times a day, conveniently once or twice a day, and most conveniently once a day.

In one embodiment of the present invention the second active ingredient is administered by inhalation. When administered via inhalation the dose of the second active ingredient will generally be in the range of from 0.1 microgram (μg) to 5000 μg , 0.1 to 1000 μg , 0.1 to 500 μg , 0.1 to 100 μg , 0.1 to 50 μg , 0.1 to 5 μg , 5 to 5000 μg , 5 to 1000 μg , 5 to 500 μg , 5 to 100 μg , 5 to 50 μg , 5 to 10 μg , 10 to 5000 μg , 10 to 1000 μg , 10 to

500 µg, 10 to 100 µg, 10 to 50 µg, 20 to 5000 µg, 20 to 1000 µg, 20 to 500 µg, 20 to 100 µg, 20 to 50 µg, 50 to 5000 µg, 50 to 1000 µg, 50 to 500 µg, 50 to 100 µg, 100 to 5000 µg, 100 to 1000 µg or 100 to 500 µg. The dose will generally be administered from 1 to 4 times a day, conveniently once or twice a day, and most conveniently once a day.

5 In another embodiment the present invention provides a pharmaceutical product wherein the molar ratio of first active ingredient to second active ingredient is from 1:1000 to 1000:1, such as from 1:100 to 100:1, for example from 1:50 to 50:1, for example 1:20 to 20:1.

10 In one embodiment, the present invention provides a pharmaceutical product comprising, in combination, a first active ingredient as defined above, and a second active ingredient as defined above, wherein each active ingredient is formulated for inhaled administration. In a further aspect of this embodiment, the pharmaceutical product is in the form of a pharmaceutical composition comprising the first and second active ingredients in admixture, and which composition is formulated for inhaled administration.

15 The active ingredients of the present invention are conveniently delivered via oral administration by inhalation to the lung and/or airways in the form of a solution, suspension, aerosol or dry powder (such as an agglomerated or ordered mixture) formulation. For example a metered dose inhaler device may be used to administer the active ingredients, dispersed in a suitable propellant and with or without an additional
20 excipient such as ethanol, a surfactant, lubricant or stabilising agent. A suitable propellant includes a hydrocarbon, chlorofluorocarbon or a hydrofluoroalkane (e.g. heptafluoroalkane) propellant, or a mixture of any such propellants, for example in a pressurised metered dose inhaler (pMDI). Preferred propellants are P134a and P227, each of which may be used alone or in combination with other another propellant and/or
25 surfactant and/or other excipient. A nebulised aqueous suspension or, preferably, solution may also be employed, with or without a suitable pH and/or tonicity adjustment, either as a unit-dose or multi-dose formulation. A suitable device for delivering a dry powder is Turbuhaler®.

30 The pharmaceutical product of the present invention can, for example, be administered: via an inhaler having the first and second active ingredients in separate chambers of the inhaler such that on administration the active ingredients mix in either the mouthpiece of the inhaler or the mouth of a patient or both (for simultaneous use); or,

where the first and second active ingredients are in separate inhalers, via separate inhalers (for separate or sequential use); or the first and second active ingredients are in admixture in an inhaler when the inhaler is supplied to a patient (for simultaneous use).

A dry powder inhaler may be used to administer the active ingredients, alone or in
5 combination with a pharmaceutically acceptable carrier (such as lactose), in the later case either as a finely divided powder or as an ordered mixture. The dry powder inhaler may be single dose or multi-dose and may utilise a dry powder or a powder-containing capsule.

Metered dose inhaler, nebuliser and dry powder inhaler devices are well known and a variety of such devices is available.

10 The combination of the present invention may be used to treat diseases of the respiratory tract such as obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary
15 disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections;
20 complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay
25 fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus.

Accordingly, the present invention further provides a pharmaceutical product according to the invention for simultaneous, sequential or separate use in therapy.

The present invention further provides the use of a pharmaceutical product
30 according to the invention in the manufacture of a medicament for the treatment of a respiratory disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis,

emphysema or bronchitis (such as chronic obstructive pulmonary disease or asthma; for example chronic obstructive pulmonary disease).

The present invention still further provides a method of treating a respiratory disease which comprises simultaneously, sequentially or separately administering:

- 5 (a) a therapeutically effective dose of a first active ingredient as defined above; and,
(b) a therapeutically effective dose of a second active ingredient as defined above;
to a patient in need thereof.

In a further aspect the present invention provides the use of a pharmaceutical product, kit or composition as hereinbefore described for the treatment of a respiratory
10 disease, in particular chronic obstructive pulmonary disease, asthma, rhinitis, emphysema or bronchitis (such as chronic obstructive pulmonary disease or asthma; for example chronic obstructive pulmonary disease).

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic"
15 and "therapeutically" should be construed accordingly. Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the condition or disorder in question. Persons at risk of developing a particular condition or disorder generally include those having a family history of the condition or disorder, or those who have been identified by
20 genetic testing or screening to be particularly susceptible to developing the condition or disorder.

The invention will now be illustrated but not limited by reference to the following Examples.

25 **Example 1**

Evaluation of compound activity on intra-alveolar neutrophil migration after aerosol challenge with lipopolysaccharide (LPS) in rats

LPS challenge in rats causes an influx of inflammatory cells into the lungs. Rats are challenged either with an aerosol of 0.9% w/v saline or 0.1-0.5 mg/mL LPS in 0.9% saline
30 for 30 min or an intratracheal dose of 0.1-10µg/kg. This is repeated up to 8 times according to the experimental protocol. Rats are dosed with vehicle, standard compound or test

compound by the appropriate route and frequency at various time points before and after challenge depending upon the experimental protocol. Test compound groups may either be the same compound at different doses or single doses of different compounds or a combination of the two. Test compounds are given by intraperitoneal, intravenous or subcutaneous injection or by inhalation or intratracheal administration.

The rats are euthanized at various time points after challenge depending upon the nature of the study, but typically 4hr after LPS challenge with 1mL pentobarbitone sodium. A tracheotomy is performed and a cannula inserted. The airway is then lavaged using 3 mL sterile PBS at room temperature. The PBS is left in the airway for 10 seconds before being removed. The PBS containing cells is placed into a 15 mL centrifuge tube on ice. This process is repeated three times.

An aliquot of BAL fluid is removed and counted on Sysmex (Sysmex UK, Milton Keynes). Cytospin slides are prepared by adding a 100 µl aliquot of BAL fluid into cytospin funnels in a Shandon Cytospin3 operated at 700 rpm for 5 min. Slides are stained on the Hema-Tek-2000 automatic slide stainer, using Wright-Giemsa stain and typically, 200 cells are counted under a microscope. Cells are classified as eosinophils, neutrophils and mononuclear cells (mononuclear cells included monocytes, macrophages and lymphocytes) and are expressed as a percentage of the total count.

Example 2

Evaluation of lung function in anaesthetised guinea-pigs

Male Dunkin-Hartley guinea-pigs (300-600g) are weighed and dosed with either vehicle or compound in an appropriate vehicle according to the experimental protocol via the intratracheal route under recoverable gaseous anaesthesia (5% halothane in oxygen).

Following dosing, the animals are administered supplemental oxygen and monitored until full recovery. Typically a dose volume of 0.5 mL/kg is used for the intratracheal route. In a dose response study, animals are dosed with compound or vehicle two hours prior to the administration of bronchoconstrictor agent (e.g. histamine or methacholine). Test compound groups could either be the same compound at different doses or single doses of different compounds or a combination of the two.

The guinea-pigs are anaesthetised with pentobarbitone (1 mL/kg of 60 mg/mL solution intraperitoneally) approximately 30 minutes prior to the first bronchoconstrictor

administration. The trachea is cannulated and the animal ventilated using a constant volume respiratory pump (Harvard Rodent Ventilator model 683) at a rate of 60 breath/min and a tidal volume of 5 ml/kg. A jugular vein is cannulated for the administration of bronchoconstrictor agent or maintenance anaesthetic (0.1 mL of pentobarbitone solution, 60 mg/mL, as required).

The animals are then transferred to a Flexivent System (SCIREQ, Montreal, Canada) in order to measure airway resistance. The animals are ventilated (quasi-sinusoidal ventilation pattern) at 60 breaths/min at a tidal volume of 5 mL/kg. A positive end expiratory pressure of 2-3 cmH₂O is applied. Respiratory resistance is measured using the Flexivent “snapshot” facility (1 second duration, 1 Hz frequency). Once stable baseline resistance value has been obtained the animals are given histamine dihydrochloride or methacholine in ascending doses (histamine; 0.5, 1, 2, 3 and 5 µg/kg, i.v., methacholine; 3, 10 and 30 µg/kg, i.v.) at approximately 4-minute intervals via the jugular catheter. After each administration of histamine or methacholine, the peak resistance value is recorded. Guinea pigs are euthanised with approximately 1.0mL pentobarbitone sodium (Euthatal) intravenously after the completion of the lung function measurements.

Percentage bronchoprotection produced by a compound is calculated at each dose of histamine or methacholine as follows:

$$\% \text{ bronchoprotection} = \frac{\% \text{ change } R_{\text{veh}} - \% \text{ change } R_{\text{cmpd}}}{\% \text{ change } R_{\text{veh}}}$$

Where % change R_{veh} is the mean of the maximum percentage change in airway resistance in the vehicle treated group.

Example 3

Evaluation of Compounds on Antigen induced Eosinophilia in Ovalbumin Sensitised Brown Norway Rats

On day 0 of the study Brown Norway rats are given a subcutaneous injection of 500 µg ovalbumin adsorbed onto 100 mg aluminium hydroxide in 0.4 mL saline in two distinct sites, approximately 0.2 mL per site. Day 14 and 15 following sensitisation the rats are challenged with aerosolised ovalbumin for 15 minutes. The rats are placed in groups of 10

in an acrylic box (internal dimensions 320mm wide x 320mm deep x 195 mm high, 20L volume). 8mL of 10 mg/mL ovalbumin in 0.9% saline, or 0.9% saline alone, is placed in each of two jet nebulizers (Sidestream®, Profile Respiratory Systems Ltd.). Compressed air at 6 L/min is passed through each nebulizer and the output of the nebulizers is passed
5 into the box containing the rats.

Rats are dosed via the appropriate route with vehicle, standard compound or test compound at various time points before and after challenge depending upon the experimental protocol. Rats are euthanised with 0.5 mL pentobarbitone sodium (Euthatal) intraperitoneally at various times after challenge. A tracheotomy is performed and the
10 trachea cannulated. The airway is then lavaged using 3 mL sterile PBS at room temperature. The PBS is left in the airway for 10 seconds before being removed. The PBS containing cells is placed into a 15 mL centrifuge tube on ice. This process is repeated three times. The final volume recovered is recorded. An aliquot of BAL fluid is removed and counted using a Sysmex (Sysmex UK, Milton Keynes).

Cytospin slides are prepared by adding a 100 µl aliquot of BAL fluid into cytospin
15 funnels in a Shandon Cytospin 3 operated at 700 rpm for 5 min. Slides are stained on the Hema-Tek-2000 automatic slide stainer, using Wright-Giemsa stain and typically, 200 cells are counted under a microscope. Cells are classified as eosinophils, neutrophils and mononuclear cells. Mononuclear cells included monocytes, macrophages and lymphocytes.

Example 4

Evaluation on the effect of compound on lung function and BAL-neutrophilia following acute smoke exposure in the mouse

BALB/c or C57BL6/J mice undergo whole body exposure to main stream smoke (50
25 min/12 cigarettes) and fresh air once or twice a day for 1-9 days. Mice are dosed via the appropriate route with vehicle, standard compound or test compound at various time points before and after challenge depending upon the experimental protocol. On the final day of the experiment, mice are either killed with euthatal 0.2 ml i.p. and broncho-aveolar lavage fluid obtained for analysis of white blood cell infiltration (as described above) or lung
30 function is assessed using a Flexivent System (SCIREQ, Montreal, Canada). Alternatively lung mechanics are measured using a forced manoeuvres system (EMMS).

Mice are anaesthetised with pentobarbitone (1/10 dilution at a dose volume of 1 mL/kg intraperitoneally). The trachea is cannulated and the animal transferred to the Flexivent System where they are ventilated (quasi-sinusoidal ventilation pattern) at a rate of 150 breath/min and a tidal volume of 10 ml/kg in order to measure airways resistance.

5 Respiratory resistance is measured using the Flexivent “snapshot” facility (1 second duration, 1 Hz frequency). Mice are euthanised with approximately 0.5mL pentobarbitone sodium (Euthatal) intravenously after the completion of the lung function measurements.

Example 5

Evaluation of bronchodilator activity in the guinea-pig isolated tracheal ring preparation.

Guinea-pigs (300-600g) are killed by cervical dislocation and the trachea removed. After clearing the adherent connective tissue, the trachea is cut into four ring segments (2-3 cartilage rings in width) and suspended in 10ml organ baths containing modified Krebs' solution (gassed with 5% CO₂, 95% O₂ at 37°C). The tracheal rings are attached to an isometric force transducer for the measurement of isometric tension. The tissues are washed and a force of 1g was applied to each tissue. Protocol A: The rings are precontracted with methacholine (1 µM) and a cumulative (10⁻⁹M – 10⁻⁵M) isoprenaline concentration effect curve is constructed. Responses are expressed as a percentage relaxation of the methacholine induced contraction. The rings are washed and a second concentration of methacholine (1µM) is added. Once the contraction has reached a plateau isoprenaline or the compound under investigation is added until a maximum effective dose is reached. Data are collected using the ADInstruments chart4forwindows software, which measures the maximum tension generated at each concentration of agonist and the response expressed as percentage relaxation.

Protocol B: A cumulative methacholine concentration effect curve is constructed and then the tissue is washed. Vehicle or test compound is added to the tissue and allowed to equilibrate. A second extended cumulative concentration response curve to methacholine is constructed. Data are collected using the ADInstruments chart4forwindows software, which measures the maximum tension generated at each concentration of agonist and the response expressed as percentage relaxation. Results are expressed as percentage of the maximum response measured in the first curve. Then, pA₅₀ values are calculated from the

first (untreated) and second (compound treated) methacholine concentration response curves and a potency value, pA_2 , was calculated.

Example 6

5 **Inhibition of lipopolysaccharide (LPS)–induced TNF α production in human peripheral blood mononuclear cells.**

Human isolated peripheral blood mononuclear cells (PBMCs) are pre-incubated with a range of concentrations of the test compound, alone or in the presence of a range of concentrations of a second compound with a distinct pharmacological activity for 18 hours
10 at 37°C. After the pre-incubation period, the cells are then incubated with LPS (1 μ g/mL) for 4 hours at 37°C to induce TNF α production. The total assay volume is 200 μ L. At the end of the incubation period, 25 μ L of the culture supernatant is analysed to quantify the TNF α released using a Fluorescence-linked immunosorbance assay (FLISA).
Fluorescence levels are read on an FMAT plate reader. Inhibition curves are fitted using a
15 4-parameter logistic equation in a non-linear curve fitting routine and activity is expressed as pIC₅₀.

CLAIMS

1. A pharmaceutical product comprising, in combination, a first active ingredient which is 3-(2-Chloro-3-((4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)-N-cyclopentyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo[
5 [b][1,4] oxazin-8-yl)ethylamino)ethyl)propanamide or a salt thereof, and a second active ingredient selected from:

an Adenosine A2A receptor antagonist;

an anti-infective;

10 a non-steroidal Glucocorticoid Receptor (GR Receptor) Agonist;

an antioxidant;

a CCR1 antagonist;

a chemokine antagonist (not CCR1);

a corticosteroid;

15 a CRTh2 antagonist;

a DP1 antagonist;

a formyl peptide receptor antagonist;

a Histone Deacetylase activator;

a chloride channel hCLCA1 blocker

20 an Epithelial sodium channel blocker (ENAC blocker)).

an Inter-cellular adhesion molecule 1 blocker (ICAM blocker);

an IKK2 kinase inhibitor;

a JNK kinase inhibitor;

a cyclooxygenase inhibitor (COX inhibitor);

25 a lipoxygenase inhibitor;

a leukotriene receptor antagonist;

a MEK-1 kinase inhibitor

a myeloperoxidase inhibitor (MPO inhibitor);

a phosphodiesterase PDE4 inhibitor;

30 a phosphatidylinositol 3 (PI3)-kinase γ inhibitor (PI 3 kinase γ inhibitor)

a peroxisome proliferator activated receptor agonist (PPAR γ agonist);

a protease inhibitor;

a p38 inhibitor

a retinoic acid receptor modulator (RAR γ modulator;

a selective glucocorticoid receptor agonist (SEGRA),

a Statin;

5 a thromboxane antagonist; or

a vasodilator.

2. A pharmaceutical product as claimed in claim 1 wherein the first active ingredient is in the form of a salt which is a sulphate or a hydrochloride, hydrobromide,
10 trifluoroacetate, sulphate, phosphate, acetate, fumarate, maleate, tartrate, lactate, citrate, pyruvate, succinate, oxalate, methanesulphonate, *p*-toluenesulphonate, bisulphate, benzenesulphonate, ethanesulphonate, malonate, xinafoate, ascorbate, oleate, nicotinate, saccharinate, adipate, formate, glycolate, L-lactate, D-lactate, aspartate, malate, L-tartrate, D-tartrate,, stearate, 2-furoate, 3-furoate, napadisylate (naphthalene-1,5-disulfonate or
15 naphthalene-1-(sulfonic acid)-5-sulfonate), edisylate (ethane-1,2-disulfonate or ethane-1-(sulfonic acid)-2-sulfonate), isethionate (2-hydroxyethylsulfonate), 2-mesitylenesulphonate, 2-naphthalenesulphonate, 2,5-dichlorobenzenesulphonate, D-mandelate, L-mandelate, cinnamate, benzoate, adipate, esylate, malonate, mesitylate (2-mesitylenesulphonate), napsylate (2-naphthalenesulfonate), camsylate (camphor-10-sulphonate), formate, glutamate, glutarate, glycolate, hippurate (2-(benzoylamino)acetate),
20 orotate, xylate (*p*-xylene-2-sulphonate), pamoic (2,2'-dihydroxy-1,1'-dinaphthylmethane-3,3'-dicarboxylate), palmitate or furoate.

3. A pharmaceutical composition which comprises a compound of the formula (I), or
25 a pharmaceutically acceptable salt thereof as claimed in claims 1-2, and a pharmaceutically acceptable adjuvant, diluent or carrier.

4. Use of a product according to any one of claims 1-3 in therapy.

30 5. Use of a product according to any one of claims 1 to 4 in the manufacture of a medicament for the treatment of a respiratory disease.

6. Use according to claim 5, wherein the respiratory disease is chronic obstructive pulmonary disease.

7. Use according to claim 5, wherein the respiratory disease is asthma.

5

8. A method of treating a respiratory disease, which method comprises simultaneously, sequentially or separately administering:

(a) a (therapeutically effective) dose of a first active ingredient which is as defined in claim 1;

10

(b) a (therapeutically effective) dose of a second active ingredient which is as defined in claim 1;
to a patient in need thereof.

15

9. A kit comprising a preparation of a first active ingredient, a preparation of a second active ingredient, both as defined in claim 1, and optionally instructions for the simultaneous, sequential or separate administration of the preparations to a patient in need thereof.

20

10. A pharmaceutical composition comprising, in admixture, a first active ingredient which is 3-(2-Chloro-3-((4-(2-ethylthiazole-4-carbonyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenethoxy)-N-cyclopentyl-N-(2-(2-(5-hydroxy-3-oxo-3,4-dihydro-2H-benzo [b][1,4] oxazin-8-yl)ethylamino)ethyl)propanamide or a salt thereof, and a second active ingredient which is selected from:

an Adenosine A2A receptor antagonist;

25

an anti-infective;

a non-steroidal Glucocorticoid Receptor (GR Receptor) Agonist;

an antioxidant;

a CCR1 antagonist;

a chemokine antagonist (not CCR1);

30

a corticosteroid;

a CRTh2 antagonist;

a DP1 antagonist;

- a formyl peptide receptor antagonist;
- a Histone Deacetylase activator;
- a chloride channel hCLCA1 blocker
- an Epithelial sodium channel blocker (ENAC blocker)).
- 5 an Inter-cellular adhesion molecule 1 blocker (ICAM blocker);
- an IKK2 kinase inhibitor;
- a JNK kinase inhibitor;
- a cyclooxygenase inhibitor (COX inhibitor);
- a lipoxygenase inhibitor;
- 10 a leukotriene receptor antagonist;
- a MEK-1 kinase inhibitor
- a myeloperoxidase inhibitor (MPO inhibitor);
- a phosphodiesterase PDE4 inhibitor;
- a phosphatidylinositol 3 (PI3)-kinase γ inhibitor (PI 3 kinase γ inhibitor)
- 15 a peroxisome proliferator activated receptor agonist (PPAR γ agonist);
- a protease inhibitor;
- a p38 inhibitor
- a retinoic acid receptor modulator (RAR γ modulator)
- a selective glucocorticoid receptor agonist (SEGRA),
- 20 a Statin;
- a thromboxane antagonist; or
- a vasodilator.

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2011/052559

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/535 A61K31/425
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 2011/012896 A2 (ASTRAZENECA AB [SE]; PULMAGEN THERAPEUTICS SYNGERY LTD [GB]; ALCARAZ L) 3 February 2011 (2011-02-03) example 33 -----	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2011/052559

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011012896 A2	03-02-2011	TW 201107335 A	01-03-2011
		US 2011053909 A1	03-03-2011
		UY 32814 A	28-02-2011
		WO 2011012896 A2	03-02-2011
